Brain Pathology ISSN 1015-6305

MINI-SYMPOSIUM: Dementia in Parkinson's Disease

Profile of Cognitive Impairment in Parkinson's Disease

G. Stennis Watson[3,5]; James B. Leverenz[1,2,4,5]

[1] Mental Illness, [2] Parkinson's Disease and [3] Geriatric Research Education and Clinical Centers, VA Puget Sound Health Care System, Seattle Division, Seattle, WA
Departments of [4] Neurology, and [5] Psychiatry and Behavioral Sciences, University of Washington, Seattle, WA

Keywords
Parkinson's disease, dementia, cognitive impairment, neuropsychology.

Corresponding author:
James B. Leverenz, MD, VA Puget Sound Health Care System, MIRECC (116MIRECC), 1660 S. Columbian Way, Seattle, WA 98108 (E-mail: *leverenz@u.washington.edu*)

Received 11 December 2009; accepted 31 December 2009.

doi:10.1111/j.1750-3639.2010.00373.x

Abstract

Cognitive impairment (CI) is a common nonmotor complication of Parkinson's disease (PD), and is associated with significant disability for patients and burden for caregivers. Similar to motor symptoms, the characteristics of CI in PD can be quite variable, both in terms of what cognitive domains are impaired, and the timing of onset and rate of progression. This review will examine the profile of cognitive domain impairments observed in PD, with a focus on early CI (without dementia). We will also discuss possible relationships between specific cognitive domain impairments in PD and pathological processes such as Lewy-related pathology and Alzheimer's disease. It is our hypothesis that the specific characteristics of CI observed in individual PD patients provide clues to the underlying pathological processes, and that understanding the biological basis of this clinical phenomenon will assist in directing disease-specific treatments. Given the high lifetime risk for CI in PD, it is imperative that we improve our understanding and treatments for this common and disabling problem in PD.

Cognitive impairment (CI), including both dementia and CI without dementia (CIND), is an increasingly recognized nonmotor complication of Parkinson's disease (PD) with significant clinical impact. CI in PD has been associated with nursing home placement, mortality and increased caregiver burden (1, 2, 29). PD with dementia (PDD) has a cross-sectional prevalence of approximately 30%, and a lifelong risk of up to 80% (3, 5, 22). CIND is also common at the time of PD diagnosis: Aarsland *et al* recently reported that 19% of their untreated PD patients had CI at the time of diagnosis (6). Thus, CI, with or without dementia, is a problem from the earliest stages of PD, and contributes significantly to the morbidity and mortality of the disease.

Despite the high lifelong risk of dementia in PD, there appears to be a relatively long period of CIND preceding the onset of dementia. Consistent with this are studies showing frequent CIND in early PD (6, 58) with a delay of up to 20 years prior to the onset of dementia (3, 22). From these data, it may be inferred that a sizable proportion of PD patients fall within the CIND group, and that the period of CIND may be quite protracted.

This review will focus on the "cognitive profile" of CI in PD, when possible focusing on CI observed prior to the onset of frank dementia. We hypothesize that the pattern of early CI in PD may provide clues to the underlying pathological processes leading to CI. We will address four areas of cognition: (i) attention and frontal-executive functions; (ii) memory; (iii) visuospatial skills; and (iv) language (see Supporting Information Table S1). We will then briefly review the potential pathological processes underlying cognitive domain impairments in PD. Ultimately, a better characterization of CI in PD and a better understanding of the underlying pathological processes will help guide successful treatment of this important nonmotor complication PD.

ATTENTION AND FRONTAL-EXECUTIVE FUNCTIONS

In the human brain, the prefrontal cortex occupies a large portion of the cortical mantle and has extensive connections to most brain regions. It is not surprising then that the prefrontal cortex regulates the flow of information that determines how an individual will behave. The prefrontal cortex allows an individual to pay attention to one event or phenomenon to the exclusion of others, as well as switch among them. It allows one to act automatically or even override automatic actions, and act in a fashion counter to biological or environmental programming. Furthermore, the prefrontal cortex facilitates reasoning. Together, these cognitive abilities are frequently grouped together as "frontal-executive" functions. Damage to the prefrontal cortex can substantially disrupt everyday functioning, while leaving many cognitive functions intact, as emphasized by the well-known case of Phineas Gage (35).

Attention is the process of filtering information related to internal and external stimuli. In general, this cognitive process can be treated as two separate processes, one that is relatively simple, bottom-up (data driven) and automatic, and a second that is relatively complex, top-down and controlled. Assessing simple attention frequently employs the digit span forward test (repeating a string of digits in the same order it was presented); simple visual scanning (trail-making test, part A, "Trails A"); or counting backward by one. These are normally effortless tasks for a cognitively

intact adult. In contrast, complex attentional and executive tasks require effort. Measures of complex attention assess divided attention (trail-making test, part B, "Trails B"); sustained attention or vigilance (continuous performance test); response inhibition (Stroop interference test, Luria motor programs); working memory (digit span reverse, serial subtraction, mental arithmetic, symbol coding); mental flexibility (Wisconsin card sorting test); planning (mazes, tower tests); and abstract reasoning (similarities, matrix reasoning). For a discussion of these individual neuropsychological tests, we refer readers to Lezak *et al*'s "Neuropsychological Assessment" (30). There is some disagreement on whether PD patients without dementia are at risk for deficits in simple attention. Although several studies have reported performance deficits on Trails A (17, 20, 21, 31), other studies have failed to find deficits in simple attention associated with mild PD (10, 20, 38, 47, 53). In contrast, numerous studies have documented deficits in complex attention. Relative to intact, same-age peers, PD patients without dementia perform more poorly on Trails B (10, 32, 38, 47, 52), and many other measures of divided attention, planning, response inhibition, working memory, mental flexibility and abstract reasoning (6, 10, 13, 17, 21, 24, 31, 39, 44).

Degradation of complex attention can be particularly troubling because it signals a decline in strategic skills that facilitate adaptive behavior. For example, Trails B assesses a person's ability to alternate between two tasks quickly and accurately, and thus demands some of the same skills as driving an automobile. A driver has to attend to the road and at the same time to other stimuli such as the radio, windshield wipers or a child in the backseat. To date, Trails B is the best pencil-and-paper instrument for estimating driving abilities, and a person who performs poorly on this test is at increased risk for reduced driving abilities (43, 51).

MEMORY

"Memory" is not a unitary construct; rather, there are multiple memory systems subserved by multiple brain structures. The case for multiple memory systems is well illustrated by the patient H.M. who underwent bilateral temporal lobe resection for intractable epilepsy (36). From studies with H.M., Dr. Brenda Milner and colleagues demonstrated that encoding of human declarative memory relies on medial temporal structures, but retrieval of declarative memories, as well as other types of memory, is independent of these structures (36).

Here, we use "memory" to refer to "long-term memory," a term used by Kolb and Whishaw to encompass emotional memory, implicit memory and explicit memory (27). Emotional memory is dependent on the amygdala, hippocampus and other brain structures to encode vivid, easily accessible, emotionally tagged information. Implicit memory is subserved by the basal ganglia, motor cortex and cerebellum. Implicit memory includes procedural memory, language learning, motor memory, priming and mirror learning. The case of H.M. clearly demonstrates that implicit memory can be spared even when there is extensive damage to medial temporal structures, and that implicit learning can take place in the absence of conscious memory of the learning event. Explicit (or declarative) memory comprises two subordinate memory systems: episodic memory, i.e. memory for information that has autobiographical relevance, and semantic memory, or memory for factual knowledge. An important difference in implicit and explicit memory is how memory is acquired. Explicit memory is acquired through top-down processes where other brain areas help direct what is to be learned. In contrast, implicit memory is acquired through bottom-up processes, where the information to be learned largely determines the memory. It is important to keep in mind that declarative memory is a multistage process influenced by other cognitive functions (see Figure 1).

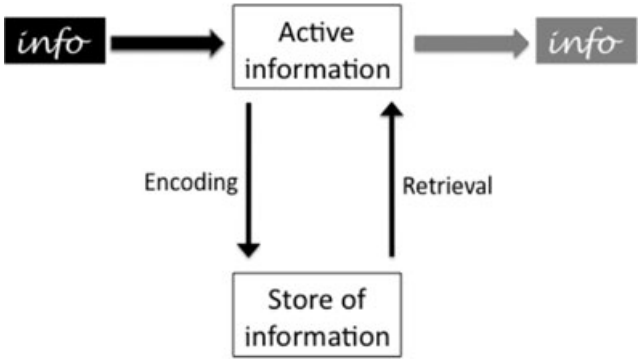

Figure 1. A simple schema for understanding declarative memory. Information to be remembered (black box on the left) must be attended to and filtered through perceptual processes (e.g. language or visuoperceptual functions) before it can enter short-term or working memory (active information). A limited amount of active information can be held in short-term memory where it is available for mental operations or behavioral responses. The hippocampus is essential for encoding, but not for storing or retrieving, declarative memories from the long-term store of information. As it is needed, information is retrieved from long-term memory (store of information) and transferred to short-term memory where it is once again available for use. Impaired attention and frontal-executive functions, which are common in Parkinson's disease (PD), are most likely to influence gathering of information into short-term memory and retrieval of information from long-term storage. Therefore, memory output should be improved when attentional demands are reduced and retrieval strategies are provided. In contrast, Alzheimer's disease reduces the amount of information encoded; improving attention and providing retrieval strategies should be less likely to help the person with Alzheimer's disease than the person with PD. A finding that immediate memory was intact and that delayed memory was impaired in a group of PD patients with cognitive impairment without dementia (CIND) would suggest an amnestic CIND subtype distinct from the expected "so-called subcortical" picture characterized by impaired attention and executive skills.

Evaluation of memory in PD patients has largely focused on explicit memory and implicit memory. A number of studies demonstrate clearly that both verbal and nonverbal explicit memory can be disrupted in PD patients without dementia. Story recall is considered to be verbal contextual declarative memory because it provides a framework for the information. Impairments in both immediate and delayed story recall have been reported in patients with PD (17, 38). Word list learning is considered to be verbal noncontextual declarative memory because a structure must be generated and imposed on the list of items to be remembered. The most common word list tasks include the California verbal learning test, Rey auditory verbal learning test and the Hopkins verbal learning test, which assess immediate recall, delayed recall and recognition. Several studies have shown that immediate and delayed wordless

learning can be impaired in early PD (6, 21, 32, 38, 51), but effects on recognition are less clear (6, 38, 47). The model presented in Figure 1 indicates that delayed memory (both story recall and word list learning) involves fundamental aspects of long-term memory: encoding, storage and retrieval. Therefore, delayed memory deficits imply dysfunction in the declarative memory system in PD patients without dementia.

Similarly, memory for nonverbal information can be impaired in PD patients without dementia. As with verbal memory, nonverbal tasks assess immediate recall, delayed recall and recognition. Common tasks used to assess nonverbal memory include facial recognition [Warrington FRT and Wechsler memory scale (WMS)—III facial recognition], figure recall (WMS visual reproduction and complex figure recall task) and the Benton visual retention test. Deficits have been reported on measures of facial recognition, figure copy and visual retention (17, 24, 38, 41, 51). Taken together, the deficits in verbal and nonverbal memory suggest that PD patients without dementia have an increased risk for memory impairments. Additionally, as summarized by Tröster (48), several studies suggest that PD patients with dementia may have impaired remote memory; however, the changes are not prominent in PD patients without dementia.

Implicit learning may be impaired in PD without dementia. In a recent study, PD patients without dementia and healthy controls were compared on measures of explicit (WMS battery), implicit (stem completion and degraded picture identification) and procedural memory (choice reaction time). PD patients and controls were equivalent on the WMS battery, stem completion and picture identification, but only the controls decreased reaction time over sequential learning trials (55). A separate group of investigators examined the role of spatial context cuing and found that controls, but not patients, responded faster on a visual search task when the visual context was repeated (53). Thus, certain types of implicit memory may decline early in mild PD.

VISUOSPATIAL SKILLS

Visuospatial skills include a number of cognitive abilities tied to the processing of visual information. This includes pattern recognition (facial recognition), constructional ability (figure drawing), color recognition (color naming) and spatial analysis (ability to perceive multiple objects in a visual field, "The Cookie Theft Picture"). Not surprisingly, posterior cortical areas have been associated with deficits in visual processing including the occipital, parietal and temporal lobes. Neuroimaging suggests that visuospatial impairment in PD without dementia is associated with posterior cortical dysfunction (7).

Numerous reports have confirmed that PD patients without dementia perform more poorly than healthy controls on visuoperceptual/visuospatial tasks with and without motor components. Specifically, deficits have been reported on judgement of line orientation (24, 32, 38, 51), facial recognition (41), form discrimination (41), reasoning (38), block construction (20, 51) and figure copy (21, 51). It was noted above that poor performance on Trails B is associated with declining driving skills. Given the visuospatial demands of driving, it seems likely that visuospatial measures would also be associated with driving abilities. Among patients with PD, efficient identification of landmarks and traffic signs has been associated with the ability to copy a complex figure, as well as visual processing speed (51). Thus, a very important and practical reason to assess visuospatial skills is to determine whether a nondemented patient with PD can safely operate an automobile.

Furthermore, the conjunction of visuoperceptual deficits and visual hallucinations may increase the risk of converting from PD without dementia to PDD (42). Ramirez-Ruiz *et al* reported that nearly 70% of their nondemented PD patients with visual hallucinations have multiple domain CIs, and that nearly half of this group converted to dementia within a year; this decline in general cognitive function was associated with specific declines in visual memory and visuospatial/visuoperceptual processing (42).

The predominance of visuospatial dysfunction in PD is further emphasized in PDD where these patients have more severe impairments on visuoperceptual measures such as drawing figures, identifying television personalities, form discrimination and visual counting than observed in Alzheimer's disease (34, 48). Although motor dysfunction may contribute to impairments on some visuospatial tasks (e.g. copying figures or constructing designs with blocks), patients with PDD have an enhanced risk for visuospatial impairments that reflect disrupted praxis and visuoperception over and above the contributions of motor dysfunction (48).

LANGUAGE

While there is a general acknowledgment that persons with PD may experience declines in attention/executive functions, memory and visuospatial skills, there is less agreement concerning language impairments. Among recent reviews of cognitive deficits and PD, some have identified language as a specific area of concern (34, 49). Others have not specified language as a separate area of concern, although they may have identified impairments in specific language functions (e.g. verbal fluency) (18, 57). One explanation for this discrepancy is that language changes are a relatively minor aspect of CI in PD. More likely, language functions known to become impaired have been assigned to other domains. For example, verbal fluency (especially phonemic verbal fluency) has been classified both as a language function and an index of executive functioning. For the purposes of this discussion, we will assume that verbal fluency assesses both language and executive skills.

Language impairments have been reported on measures of phonemic verbal fluency (51), semantic verbal fluency (6) and visual confrontation naming (12). Verbal fluency tests a person's ability to name all the words that he or she can produce in 1 minute that begin with a certain letter (phonemic) or belong to a certain category (semantic). It appears that semantic verbal fluency is affected more in Alzheimer's disease, whereas the converse is thought to be true for the "so-called" subcortical dementias, including PDD (49).

In addition to traditional scoring methods, error analyses may further elucidate PD-related changes in language. For example, successful verbal fluency performance capitalizes on both clustering and switching (49). Clustering refers to strategic grouping of responses along an appropriate dimension. In a semantic verbal fluency task, clustering may take the form of supplying several ordinate level responses following a person's superordinate level response (e.g. dog followed by Irish setter, German shepherd and Labrador retriever). Switching refers to replacing a suboptimal retrieval strategy with a more productive strategy (i.e. switching from dog to bird when one has expended the easy responses to

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dog). It has been observed that patients with PDD use switching less effectively, and they use semantic clustering more effectively than do and patients with Alzheimer's disease (50). Approaches such as this response style analysis may help identify novel language impairments in PD patients without dementia.

POTENTIAL PATHOLOGICAL PROCESSES UNDERLYING COGNITIVE DOMAIN IMPAIRMENTS

While the attention and frontal-executive functions appear to be the predominant cognitive domains affected in PD, it is clear from the previous sections that the pattern of cognitive domain impairments in PD is complex. In fact, some PD patients exhibit relatively isolated impairments in memory, while others in frontal-executive or visual–spatial function (24, 25). This suggests that the neuropathological substrates of CI in PD may also be variable. Studies on the neuropathological basis of CI in PD are still somewhat limited.

An important issue in reviewing the literature on the neuropathological substrates of CI in PD is variable methodologies used to evaluate the pathological changes. For example, α-synuculein immunohistochemistry to visualize Lewy bodies has only been available for the last 10 years (9, 46). Neuropathological studies prior to that time may have missed Lewy-related pathology (LRP) in regions such as the limbic system and neocortex. In addition, there have been changes in the criteria used to pathologically diagnose Alzheimer's disease. Neuropathological confirmation of AD now necessitates the presence of both sufficient neuritic plaque and neurofibrillary tangle pathology (40). In the past, some studies, using criteria available at that time, diagnosed coexistent neuropathological AD based solely on the severity of cortical plaque pathology (26, 37). In recent years, there has also been further refinement of the clinical diagnosis of PDD, versus other similar clinical syndromes such as dementia with Lewy bodies. Currently, the clinical criteria for PDD require the presence of motor parkinsonism precede dementia by at least a year (the so-called "one year rule") (16). In the past, some studies selected patients on the basis of the coexistent parkinsonism and CI without regard to the timing of the onset of these symptoms. Thus, cases with dementia preceding parkinsonism were included in the analysis of the neuropathological basis of dementia in PD, when current criteria would classify these cases more accurately as dementia with Lewy bodies (33). These are important considerations when evaluating studies of the neuropathological basis of dementia in PD.

Taking into account these more stringent criteria (i.e. motor parkinsonism preceding dementia and use of up-to-date neuropathological methods and criteria), there appears to be a general consensus that dementia in PD is linked to anatomically diffuse LRP including the presence of LRP in the brain stem, limbic system and neocortex (4, 8, 11, 19, 23). The occurrence of coexistent AD, long thought to be the primary cause of dementia in PD, appears to be relatively uncommon in those studies of well-selected PDD cases using modern neuropathological techniques and criteria for AD. However, there is some disagreement between investigators on the frequency of AD in PDD. Galvin *et al* (19) found a sizable portion, 38%, of their PDD cases to have pathological AD, while other studies have generally found coexistent AD in less than 10% of PDD patients (4, 8, 11, 23, 33). One clear point is that the number of reported PDD cases with appropriate clinical and pathological evaluation is low, and further study of this issue is necessary to fully understand the contribution of AD to dementia in PD.

The contribution of other pathological changes to CI in PD is unclear. Vascular disease is an important primary and co-contributing cause of dementia in the elderly (45, 56). Unfortunately, there is little to no data on the presence of vascular pathology in PD, and its influence on CI. Recent evidence has linked the presence of TDP-43 pathological change to Lewy body disorders (54). However, the clinical significance of this pathology, typically linked to frontotemporal dementia and amyotrophic lateral sclerosis, has not been determined.

It is not surprising that, given the limited characterization of neuropathological changes associated with PDD, the relationship between specific pathological changes and the profile of cognitive domain impairments in PD is poorly understood. However, one can hypothesize on possible associations between pathological processes and cognitive domain impairments in PD, and propose both clinical and pathological tools that can be used to further elucidate these relationships. Generally, dementia in patients with relatively isolated LRP is associated with attention and frontal-executive dysfunction, while LRP in the context of AD is associated with more severe memory impairments (28). Thus, it would be reasonable to expect that those PD patients with relatively isolated LRP (e.g. without coexistent AD) should have more prominent attention and frontal-executive dysfunction, while the subset with coexistent LRP and AD would have more prominent memory impairment. Similarly, it might also be expected that there may be distinct cognitive domain impairments, or behavioral disturbances, linked to the presence of vascular lesions or TDP-43 pathology.

Until additional neuropathological studies are available, we will likely need to evaluate this hypothesis using other modalities such as biomarkers. To date, the results from the measurement of α-synuclein in blood and cerebrospinal fluid (CSF) have been variable, although there appears to be some evidence of reduced levels of CSF α-synuclein in PD patients (15). The evaluation of AD pathology using radiolabeled ligands such as the Pittsburgh compound B (PIB) has shown relatively normal levels of PIB uptake in PDD, although the relationship to specific cognitive domain impairments has not been examined (14). Similarly, CSF levels of amyloid beta peptide (Aβ) and tau are generally found to be normal in PD and PDD (15). One study using structural imaging failed to find an association between medial temporal atrophy and memory impairment in PD (32). It remains to be seen whether the subset of PD patients with positive AD biomarkers such increased PIB binding, medial temporal lobe atrophy or altered CSF tau or Aβ have, in fact, more severe memory impairment. What is clearly needed is additional study of cognitive domain impairments in PD and the association with these disease biomarkers.

CONCLUSION

The clinical importance of CI in PD is quite evident. In addition, similar to motor impairment, there appears to be variability in the profile of CI, and the timing and progression of CI in PD. We hypothesize that the presence of multiple pathologies in PD could account for this variability. Some tools, such as imaging and biofluid markers, are now available to start to test this hypothesis. This is not just an academic question, because understanding the bio-

logical processes leading to CI in PD will have an important role in directing disease-specific treatments in the future.

ACKNOWLEDGMENTS

This work was supported by the Department of Veterans Affairs and NIH/NIA: P50MS062684-01A1, K01 AG023640.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Table S1. Summary of cognitive domains, impaired cognitive functions and representative cognitive tests.

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